FDA Workshop on Plasma Standards

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America's Blood Centers (ABC)

- ABC is a national network of locally controlled, non-profit community blood centers that provide half of the U.S. blood supply from volunteer donors.
- Its 76 members operate in 45 states and the Province of Québec, Canada.
- ABC's total blood collections exceeded 7.6 million donations in 2003.
- Every year, ABC members ship over 1 million liters of plasma from volunteer donors for manufacture into plasma therapeutics.

Major Issues Raised by FDA

- Licensure of “Recovered Plasma”
  - Product Name
  - Expiration date
  - Distinction from “Source Plasma”
- Freezing parameters
  - Time to freeze
  - Freezing rate
  - Storage temperature

Why License?

- Recovered plasma is the only blood product for interstate commerce that is not licensed and does not require FDA approvals prior to manufacture or shipment.
- It is regulated through “short supply agreements” between the supplier and the manufacturer of plasma therapeutics.
- The specifications are part of a product master file maintained by the manufacturer.
- The concept was created in the 1970’s, when plasma was literally “recovered” from expired whole blood and manufactured into albumin and other products.

Why License?

- At that time, FDA regulations were based on “intent” prohibited the conversion of Fresh Frozen Plasma to Recovered Plasma prior to its outdating because this was not the “intent” of collection
- FDA has been more flexible recently and allowed conversion of FFP to plasma for manufacture prior to its outdating.
- Plasma collected by apheresis or collected concurrently with platelet or RBC apheresis are treated differently from FFP and cannot be shipped for manufacture (except for WNV variance)

Why License?

Today's recovered plasma is prepared from whole blood collections much before expiration, after the blood center has fulfilled patient needs for transfusion. RBC collections drive blood center activities.

Plasma for transfusion produced under FDA license constitutes about 25% of all the plasma produced by blood centers.

Although the name "recovered plasma" implies a lower quality, in fact, recovered plasma generally has higher protein content and higher levels of IgG than Source Plasma. It has lower levels of Factor VIII.

- Hellstern et al. Transfusion, 2001;41:1601-1605

Why License?

- The name “recovered plasma" suggests that it is a by-product not subjected to blood cGMPs (21 CFR 640). It is inconsistent with the strict regulation of whole blood and of source plasma.
- There is FDA oversight of manufacturers of plasma derivatives
- There is no formal inspection or pre-approval of the licensed establishment to ship plasma for fractionation

ABC Position

- ABC members fully support the AABB proposal
- Plasma that is good for transfusion into a patient is good for further manufacture!
- Plasma for transfusion collected from whole blood or by apheresis that exceeds the needs of patients should be used as plasma for manufacture.
- Donors deserve optimal use of the products that they donated voluntarily; if not used for fractionation, most of the plasma from whole blood would be discarded. They would be furious if they knew that part of their donation was discarded

Should We Inform Donors?

- Yes
- Collecting facilities would include a statement in the informed consent indicating that the plasma from their donation may be used for the manufacture of medications such as albumin and IVIg

Should Plasma for Manufacture be Distinguished from Source Plasma?

- Yes
- Should be distinguished by frequency of donation, not by intent of donation
- Donors of Source Plasma are frequent donors and should be regulated as such
- Donors of Whole Blood, Platelets and Plasma are infrequent donors and should be regulated as Whole Blood Donors

What Should be the Standards?

- Should be the same for plasma for transfusion and plasma for manufacture
- What is good for a patient is good for fractionation
- AABB included recovered plasma in its *Standards for Blood Banks and Transfusion Services*
- Blood banking organizations and the Plasma Protein Therapeutics Association (PPTA) have been working on voluntary standards
- Additional specifications should be left to the manufacturers, based on their needs and validated procedures

Freezing, Storage and Shipping Temperatures

- FDA has issued a proposed rule that changes radically the current requirements
- The new requirements demand substantial investment in money and effort by collecting facilities, shippers and fractionators
- What has prompted the change? What is wrong? Is there a new safety issue?
- Harmonization with what rules? (Council of Europe, European Pharmacopoeia, Australia, etc.)

Is There a Problem with Current Procedures?

- The vast majority of plasma for fractionation is used in the manufacture of stable proteins.
- There is a decline in Factor VIII activity with increase in time to freeze, and time in storage. There is a change in yield, but no documented change in efficacy
- Fresh Frozen Plasma is not indicated for the replacement of Factor VIII.
- A recent FDA Workshop suggested no direct correlation between the type of plasma used and the development of inhibitors in patients with hemophilia.
- Plasma for transfusion is not used to replace labile components; appropriate factor concentrates and recombinant factors are used for this purpose.

Is There a Problem with Current Procedures?

- A multicenter study carried out in Germany concluded that storage of plasma for 36 months at -20 ^{0}C, -25 ^{0}C, -30 ^{0}C and -40 ^{0}C showed ***no detectable changes in plasma proteins***
  - Kotitschke *et al*. Stability of Fresh Frozen Plasma. Infus Ther Transfus Med 2000;27-174-180

Is There a Problem with Current Procedures?

- There is no clear reason why preservation of Factor VIII activity should drive the standards, when it is a minor product
- Manufacturers specify the requirements according to their validated procedures
- They will use the best available product to fulfill their needs, e.g.
  - Octapharma uses FFP prepared within 8 h for the manufacture of Solvent Detergent Plasma in Europe
  - ZLB uses plasma up frozen up to 120 hours for the manufacture of IVIg

Summary

- FDA should allow the use of all plasma that is good for transfusion to plasma for manufacture
- ABC members support the AABB proposal for plasma for manufacture
- Source plasma is distinguished from plasma for manufacture (recovered) by frequency of donation
- FDA should focus its regulatory efforts on donor safety, donor qualification, and cGMP, including labeling to indicate expiration date, anticoagulant, time to freeze, freezing and storage temperature
- There is no compelling reason to change requirements for freezing and storage conditions

Essentially,

If it ain’t broke, don’t fix it

America's Blood Centers

Thank you!

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